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Continuous stimulation of dopaminergic receptors by rotigotine does not interfere with the sleep–wake cycle in the rat

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Abstract

Rotigotine is a new, non-ergoline dopamine receptor agonist developed for the treatment of Parkinson's disease in a transdermal formulation (Neupro ®) to provide sustained drug delivery for 24 h with a once daily dosing. The aim of the present study was to determine whether or not continuous dopaminergic stimulation can interfere with the sleep–wake cycle. To achieve this, rotigotine was administered as a slow release formulation to provide stable plasma and brain levels over a period of 6 days and the sleep–wake cycle was evaluated in the freely-moving male rat using electroencephalagraphic recording. For comparison, the mixed dopamine/noradrenaline reuptake inhibitor nomifensine (16 mg/kg p.o.) was administered once daily for 6 days. In contrast to nomifensine, rotigotine (0.5 and 5 mg/kg s.c.) had no clear effects on the sleep–wake cycle. Nomifensine delayed the onset of rapid eye movement (REM) sleep and, to a lesser extent, also that of slow wave sleep (SWS). In addition, it increased the duration of waking time and decreased the duration of SWS and REM sleep. These effects were observed on all days and repeated administration lead neither to potentiation nor attenuation of the effects. It is concluded that a continuous dopaminergic stimulation of dopamine receptors by rotigotine may not only be beneficial for the treatment of the motor symptoms of Parkinson's disease but also have additional benefits by not compromising either sleep architecture or circadian rhythm.

Keywords: Rotigotine; Parkinson's disease; Sleep; Continuous dopaminergic stimulation; Dyskinesia; Nomifensine

1. Introduction

Parkinson's disease is a progressive neurodegenerative disease characterised by movement disturbances and therefore classified as a movement disorder. Although the motor symptoms such as tremor, rigidity of skeletal muscles and bradykinesia are its most characteristic features and essential for its diagnosis, other symptoms such as depression, cognitive impairment, dysfunction of the autonomic system and also sleep disturbances are frequent and can be as incapacitating as the motor symptoms (Ferreri et al., 2006; Gómez-Esteban et al., 2007). A wide spectrum of sleep disturbances is found in Parkinson's disease patients. Although the same disturbances are also reported in the general population, Parkinson's disease patients are more often affected than age-matched controls. Shortening of total sleep duration, fragmented sleep, rapid eye movement (REM) sleep disturbances, decrease in sleep efficiency and excessive daytime sleepiness are common in non-treated Parkinson's disease patients (Wetter et al., 2000; Gagnon et al., 2002). Some disturbances are inherent to the disease, others are thought to be induced by drug treatment or are combinations of both (Abdelgabar and Sharma, 2003). For example, dopaminergic treatment can aggravate both insomnia and daytime sleepiness (Arnulf et al., 2002; Borek et al., 2006). A form of excessive daytime sleepiness has been described as "sleep attacks" which appear to be associated more frequently with dopamine D_2 receptor agonists than with other dopaminergic treatments, but no risk factors have been established to date (Ferreira et al., 2000; Hobson et al., 2002; Homann et al., 2002).

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Most current medications for Parkinson's disease are focused on the reinstatement of dopaminergic neurotransmission. With all pharmacologic treatment approaches, however, patients are sooner or later faced with complications such as loss of drug efficacy and fluctuation of the effects, known as "on–off" phenomena, development of dyskinesia and other motor symptoms. These problems are thought to be caused in part by the discontinuous or pulsatile stimulation of dopamine receptors in the brain during oral treatment and in part by disease progression (Chase et al., 1998). Unlike the physiological oscillation of dopamine levels in the brain over 24 h which has been estimated directly in the animal brain (O'Neill et al., 1983, Smith et al., 1992) or indirectly from plasma levels in man (Markianos and Backman, 1976; Sowers and Vlachakis, 1984), Parkinson's disease medication causes both over- and under-stimulation of dopamine receptors leading to receptor sensitization and/or shifts in receptor expression and distribution (Chase et al., 1998). Although the pathophysiological mechanisms mostly have been studied on the motor system, pulsatile dopamine receptor stimulation may also underlie sleep disturbances.

It is a matter of debate which dopaminergic neurones are involved in the control of the sleep–wake cycle. A recent study showed that dopaminergic neurones in the ventral periaqueductal gray matter may play an important role in arousal (Lu et al., 2006). In contrast to dopaminergic neurones in the substantia nigra and ventral tegmental area cells, dopaminergic neurones in the periaqueductal gray matter increase their firing rate during waking and furthermore show reciprocal connections with the sleep–wake regulatory system. Although the overall firing rate of dopaminergic neurones in the substantia nigra and the ventral tegmental area does not change over the sleep–wake cycle (Miller et al., 1983), the firing pattern can change with various vigilance levels. Neurones in ventral tegmental area were found to discharge in bursts during waking with consecutive increase in dopamine release (Monti and Monti, 2007). So far, the potential effects of a continuous versus a pulsatile administration of a dopaminergic compound on the different responses of different cell populations have not been investigated. However, different therapeutic approaches have been pursued to achieve a steady activation of central dopaminergic receptors in order to omit motor complications but they have proved either to be impractical or no more efficient than other treatments (Pfeiffer, 2005). A promising recent approach was the development of a dermal administration system, a patch, providing a sustained transdermal delivery of the non-ergoline dopamine agonist rotigotine (Neupro®). Clinical studies have shown improvements of motor symptoms compared with placebo treated patients (Grosset, 2006). However, the effects of a continuous administration of rotigotine on the sleep–wake cycle have not been studied, neither in an experimental nor in clinical setting.

Because of the potential advantages of a continuous drug administration in Parkinson's disease which is likely to be increasingly used in the clinic, it is important to evaluate such approaches in all areas of importance for Parkinson's disease, including potential effects on the sleep–wake cycle, for the reasons described above. The objective of this study was, therefore, to determine whether or not continuous stimulation of dopaminergic receptors by rotigotine at doses previously shown to be active in animal models (Bertaina-Anglade et al., 2006) has an impact on the sleep–wake cycle. Direct dopamine D_1 and D_2 receptor agonists, dopamine reuptake inhibitors and the dopamine precursor 3,4-dihydroxy-L-phenylalanine (L-DOPA) have all been shown to interfere with sleep in the rat (Galarraga et al., 1986; Lelkes et al., 1987; Monti et al., 1990; Isaac and Berridge, 2003). For the present study, rotigotine was administered in the form of a slow release formulation which mimics the clinical administration providing stable plasma and brain levels in the rat for more than 48 h following subcutaneous injection (Scheller and Kehr, 2005; Kehr et al., 2007). Nomifensine was used as a positive comparison compound; it primarily served as an intrinsic control and to demonstrate that the test system was sensitive to a compound with known wake-promoting effects; it was not intended to be used for an investigation of the potential role of dopaminergic mechanism in sleep control which would be the goal of a successive study.

2. Materials and methods

2.1. Animals

Adult male Wistar (Han) rats, weighing 315–375 g at the time of surgery were used. Under pentobarbital anaesthesia (55 mg/kg i.p.) two miniature titanium screws were placed bilaterally over the fronto-parietal cortex, and two platinum-iridium depth electrodes were placed stereotaxically into the left hippocampus CA3 area. Two additional wire electrodes were implanted into the neck muscles for recording electromyographic (EMG) activity. A screw fixed over the right parieto-occipital cortex served as ground electrode. The electrodes were secured to the skull with dental acrylate. One day after surgery the animals were transferred to the recording environment, a noise-protected, ventilated and temperature controlled room, kept under a shifted light/dark cycle (lights off between 10h15 and 22h15). Recordings were started after at least 10 days of habituation.

2.2. Drugs

A slow release formulation of rotigotine ((−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]1-naphthalenol; Neupro®) and its vehicle (the oily base without drug) was supplied by Schwarz Pharma at two concentrations which could be injected s.c. to provide 0.5 or 5 mg/kg/48 h. A single injection of the suspension slowly releases the compound and provides sustained brain levels (Kehr and Scheller, 2005) which can be maintained over a prolonged period of time upon re-injection once every 2nd day. Nomifensine maleate was purchased from Sigma-Aldrich Chemicals and suspended in 0.2% hydroxymethylcellulose in distilled water. Nomifensine was given orally at 16 mg/kg each day. The dosing and administration regimen of both drugs was chosen based on previous observations demonstrating that nomfensine increased waking (unpublished Porsolt & Partners Pharmacology data) and that rotigotine enhanced locomotor activity (Scheller et al., 2005a,b) under the conditions used here.

Table 1
Effects of rotigotine and nomifensine on the latency to SWS onset

	Rotigotine 0.5 mg/kg s.c		Rotigotine 5 m/kg s.c.		Nomifensine 16 mg/kg p.o.	
Day	*n*		*n*		*n*	
Pre-test	8	38.8±13.0	8	49.1±13.1	7	25.4±12.6
1	8	17.9±3.4	8	44.9±26.4	7	163.1±91.0
2	6	43.7±16.6	8	91.4±45.2	7	213.3±88.6
3	8	23.6±6.4	8	115.8±38.7	7	296.3±106.1
4	8	77.9±22.8	8	39.4±17.9	7	161.4±88.0
5	8	19.8±8.8	7	30.9±15.1	6	179.0±86.6
6	8	40.1±12.7	8	38.3±9.1	7	261.1±92.8

Latency values (min) are shown as means±S.E.M.

2.3. Experimental procedure

Data were recorded for 8 consecutive days, with data acquisition starting at 10h15 and lasting for 23 h each day. Drug or vehicle was administered between 10h00 and 10h15 (i.e. immediately before the dark phase). The first two days were baseline recordings without and with vehicle administration respectively. The data reported as control values is the mean of these two days. Thereafter, rotigotine was administered once every second day at 0.5 or 5 mg/kg s.c. and nomifensine daily at 16 mg/kg p.o., both at a volume of 5 ml/kg. The rats had free access to food and tap water during the whole experimental period.

All surgical and experimental procedures were performed in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, Strasbourg, 18.III.1986 and were covered by a valid license to experiment on vertebrate animals issued by the French authorities.

2.4. Data recording and analysis

Electroencephalographic (EEG) signals were transferred by cable via turning commutators to a signal conditioning system (7P5/DA or P511 units from Astromed-Grass, West Warwick, RI 02893, US). Filter settings were, depending on the units, 1–75 Hz or 1–100 Hz for the cortex, 1–35 Hz or 1–30 Hz for the hippocampus and 10–3000 Hz for the neck muscle. The differential output of the cortical, hippocampal, and muscle leads were then digitized at a sampling rate of 256 Hz/channel using ECLIPSE® and RHYTHM® software (both Stellate Systems, Montreal, Canada). The signals were then spectrally analyzed over 2 s epochs, which were averaged over 10 consecutive epochs for selected frequency bands, each therefore covering 20 s of real time EEG. The data were then further processed by the program RATS® (Stellate Systems) to create hypnograms which were then analyzed in EXCEL®. The following parameters were derived from the data: a) slow wave sleep (SWS) and REM sleep latencies, defined as the time interval from the start of the data acquisition to the appearance of at least 1 min uninterrupted SWS or 40 s REM sleep; b) the time spent in one of the three vigilance states (waking, SWS and REM sleep) for selected time intervals, 0–12 and 12–23 h and for the total 23 h recording; c) The proportion of active (activity clearly above background level in the EMG lead was used to define active waking) and quiet waking within total waking; d) the number of REM phases (defined as transitions from SWS to REM sleep).

The scoring system for attribution of sleep stages was based on the following principles. High activity in the muscle leads defined active waking, whereas low activity in the muscle lead

Table 2
Effects of rotigotine and nomifensine on the latency to REM sleep onset

	Rotigotine 0.5 mg/kg s.c		Rotigotine 5 m/kg s.c.		Nomifensine 16 mg/kg p.o.	
Day	*n*		*n*		*n*	
Pre-test	8	96.4±23.1	8	142.2±29.0	7	99.6±18.7
1	8	156.5±60.1	8	289.0±138.7	7	662.7±211.9[a]
2	6	157.8±29.4	8	151.9±48.9	7	518.3±159.0[a]
3	8	210.3±106.4	8	325.1±58.1[a]	7	514.9±100.9[b]
4	8	202.5±95.3	8	186.9±45.7	7	415.7±148.2
5	8	75.0±21.0	7	111.3±26.4	6	558.0±158.8[a]
6	8	120.1±23.7	8	128.5±53.1	6	446.8±99.5[a]

Latency values (min) are shown as mean±S.E.M.
[a] $P<0.05$, [b] $P<0.01$ (repeated measures ANOVA followed by Student's *t*-test compared to control values).

Table 3
Effects of rotigotine and nomifensine on the percentage of time spent awake during each day

	Rotigotine 0.5 mg/kg s.c.		Rotigotine 5 m/kg s.c.		Nomifensine 16 mg/kg p.o.	
Day	*n*		*n*		*n*	
Pre-test	8	43.3±2.4	8	47.1±2.5	7	39.7±1.4
1	8	46.0±4.6	8	52.9±3.8	7	58.4±3.5[c]
2	6	45.9±2.6	8	47.4±3.3	7	61.7±6.6[b]
3	8	43.7±1.8	8	47.3±5.5	7	65.2±3.4[c]
4	8	44.0±5.0	8	44.1±2.3	7	58.3±2.2[c]
5	8	40.7±3.1	7	47.1±1.6	6	54.9±6.9
6	8	40.7±2.5	8	47.2±3.5	6	61.6±7.4[a]

The percentage of time spent awake per day is shown as mean±S.E.M. [a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$ (repeated measures ANOVA followed by Student's *t*-test compared to control values).

Table 4
Effects of rotigotine and nomifensine on the percentage of time spent in SWS each day

	Rotigotine 0.5 mg/kg s.c.		Rotigotine 5 m/kg s.c.		Nomifensine 16 mg/kg p.o.	
Day	*n*		*n*		*n*	
Pre-test	8	49.2±2.1	8	46.5±2.2	7	52.7±1.6
1	8	47.7±3.5	8	41.8±3.3	7	38.0±2.7[b]
2	6	48.6±2.2	8	46.9±3.2	7	33.4±5.6[b]
3	8	49.5±2.3	8	47.9±5.4	7	31.4±2.9[c]
4	8	47.2±4.0	8	49.1±2.1	7	36.6±2.5[c]
5	8	51.4±2.6	7	46.4±1.6	6	41.1±7.1
6	8	51.9±1.5	8	45.4±3.3	7	34.0±7.0[a]

The percentage of time spent awake per day is shown as mean±S.E.M.
[a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$ (repeated measures ANOVA followed by Student's *t*-test compared to control values).

Table 5
Effects of rotigotine and nomifensine on the percentage of time spent in REM sleep each day

	Rotigotine 0.5 mg/kg s.c.		Rotigotine 5 m/kg s.c.		Nomifensine 16 mg/kg p.o.	
Day	*n*		*n*		*n*	
Pre-test	8	5.9±0.9	8	5.2±0.6	7	5.9±1.0
1	8	4.9±1.9	8	4.2±0.9	7	2.5±1.0[b]
2	6	5.9±0.9	8	4.6±0.5	7	3.6±1.2
3	8	5.6±1.2	8	3.8±0.7	7	2.3±0.8[b]
4	8	7.5±1.2	8	5.7±1.5	7	3.9±1.0
5	8	6.5±0.7	7	5.5±0.6	6	2.6±0.8[c]
6	8	6.3±1.4	8	6.2±0.8	7	2.9±1.1

The percentage of time spent awake per day is shown as mean±S.E.M. [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ (repeated measures ANOVA followed by Student's *t*-test compared to control values).

combined with low delta and low alpha activity (1.5–4.5 and 8–12.5 Hz frequency bands) in the cortical lead defined quiet waking. High theta activity (4.5–7.5 Hz frequency band) in the hippocampal lead with concomitant low delta and low alpha activity in the cortical lead defined REM sleep. High delta and high alpha activity in the cortical lead and low activity in the muscle lead defined slow wave sleep. For the scoring procedure, the spectral activity for the individual leads were displayed on a computer screen and discrimination levels were visually adjusted.

For statistical analysis, one-way ANOVA with repeated measures was performed for each parameter with recording day as repeated measure. In the event of a significant ANOVA, paired Student's *t*-tests were used to compare the differences between the baseline (average of the two control recordings) and test days following drug treatment.

3. Results

Compared with pre-administration control values, rotigotine at both doses tested, 0.5 or 5 mg/kg s.c. had no clear effects on the latencies to onset of SWS or REM sleep (Tables 1 and 2). Although statistical analysis indicated a significant overall effect on delay to SWS onset at 0.5 mg/kg, none of the pair-wise comparisons with pre-administration values for individual days showed significance and none of the changes appeared systematic. In contrast, nomifensine at 16 mg/kg p.o. clearly and significantly increased the latency to onset of REM sleep

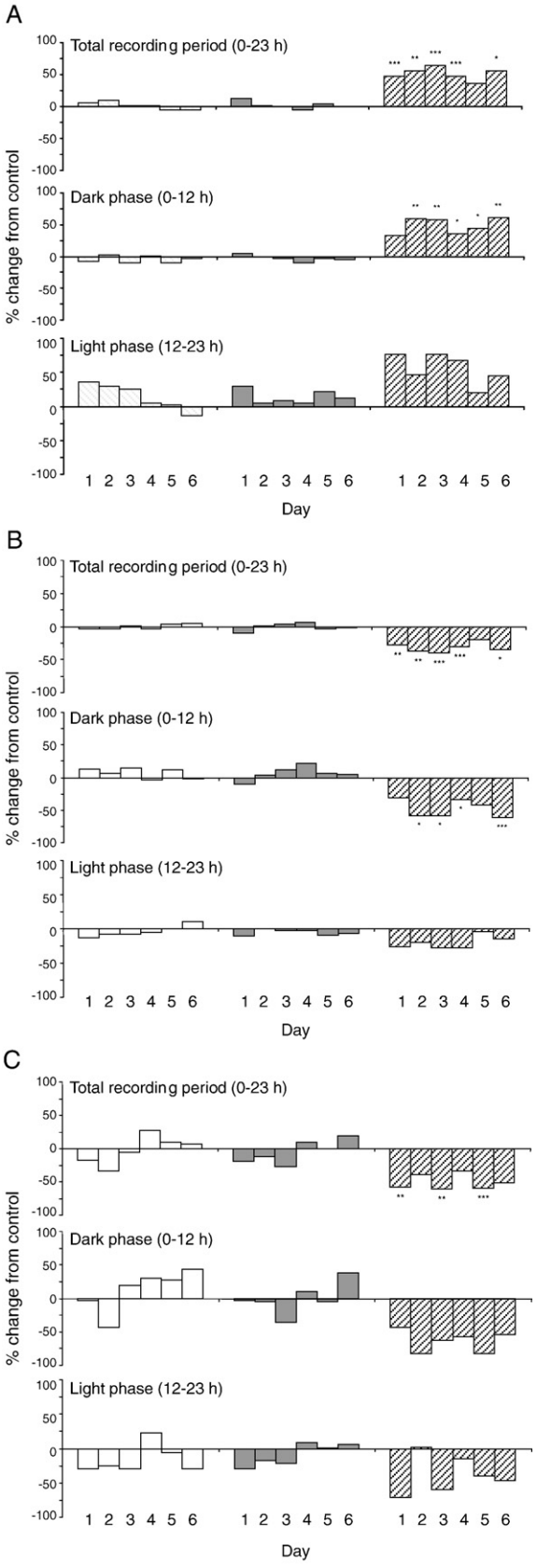

Fig. 1. Effects of rotigotine and nomifensine on the proportion of (A) waking, (B) SWS and (C) REM sleep over the 23 h of sleep–wake cycle recording and separately for the light and dark phases. Open and grey columns show data for rotigotine (0.5 and 5 mg/kg s.c. respectively); hatched columns show data for nomifensine (16 mg/kg p.o.). Data is expressed as the mean percentage change compared to pre-treatment control values for the six days of drug administration. Rotigotine was administered s.c. 15 min before the start of recording on days 1, 3 and 5. Nomifensine was administered p.o. 15 min before the start of recording every day. The graphs indicate the mean for 6 to 8 rats. Data was analysed using one-way ANOVA with repeated measures followed by paired Student's *t*-test (drug effect vs. control sessions) if the ANOVA was significant ($P<0.05$):*$P<0.05$; ** $P<0.01$: *** $P<0.001$ (compare Tables 3, 4, and 5 'Total recording period (0–23h)').

and showed a non-significant tendency to increase latency to SWS (Tables 1 and 2).

Assessed over the total sleep–wake cycle, neither dose of rotigotine had any significant effects on total waking (Table 3), SWS (Table 4) or REM sleep duration (Table 5) on any of the six days of testing compared to pre-treatment values. In contrast, nomifensine significantly increased the duration of waking, and decreased the duration of both SWS and REM sleep on most of the days tested (Tables 3–5).

When the data is analysed separately for the light phase and dark phase, there are still no clear and consistent effects of rotigotine, at either dose, on time spent awake (Fig. 1A), SWS duration (Fig. 1B) or REM sleep duration (Fig. 1C). In contrast, the effects of nomifensine are broadly consistent with the effects seen over the whole testing phase, apart from the decrease of SWS duration which is largely confined to the dark phase (Fig. 1). Analysis of the data in 4-hour blocks broadly confirms this picture, with many of the effects of nomifensine being most evident during the first 8 h after drug administration (data not shown).

The number of REM phases assessed over the total sleep–wake cycle was not significantly changed following rotigotine administration at either dose. In contrast, nomifensine significantly decreased the number of REM phases, probably as a result of the greater time spent awake.

None of the treatments significantly affected the amount of active waking as a proportion of total waking time, either when measured over the total 0–23 h recording period or for the shorter time intervals (data not shown).

4. Discussion

There are many observations, clinical as well as experimental, indicating an important role for dopaminergic neurotransmission in the regulation of vigilance and sleep dynamics (Wisor et al., 2001; Jones, 2005; Berridge, 2006; Dzirasa et al., 2006). The mechanisms of dopamine-mediated arousal and sleep control appear to be very complex. On the one hand, there are the stimulant drugs such as amphetamine, cocaine and methylphenidate which enhance dopaminergic but also noradrenergic neurotransmission; nomifensine, a stimulant antidepressant, can be considered as belonging to that group of compounds, too, as it inhibits the reuptake of both dopamine and noradrenaline (Schacht et al., 1982; Keller et al., 1982) and has repeatedly been shown to promote wakefulness in various species such as rat, cat, dog and also humans (Keller et al., 1982; Lelkes et al., 1987; Nicholson et al., 1986; Nishino et al., 1998). On the other hand, arousal can also be induced, however, by selectively interacting with either the dopaminergic or the noradrenergic neurotransmitter system on their own by stimulating dopamine D_1 and D_2 receptors (Isaac and Berridge, 2003) or α_1- and β-adrenoreceptors, respectively (Berridge, 2006).

Here we used rotigotine, a non-ergoline dopamine receptor agonist which structurally resembles dopamine and exhibits a similar binding profile; however, its affinity to dopamine receptors is about 30-fold higher than that of dopamine (Jenner, 2005; Scheller et al., 2006b). Rotigotine preferentially binds to dopamine D_3 receptors with a K_i value in the sub-nanomolar range, to dopamine D_2 receptors in the low nanomolar range and with a lower affinity to dopamine D_1 receptors. In addition, rotigotine exhibits considerable affinity for $5HT_{1A}$ receptor and the α_{2B}-adrenoreceptor (Scheller et al., 2006b). Central nervous system effects of rotigotine have been clearly demonstrated in both rodents and primates (Löschmann et al., 1989; Belluzzi et al., 1994; Bertaina-Anglade et al., 2006; Rose et al., 2007; Scheller et al., 2007).

In view of the clear evidence that dopamine is implicated in vigilance control, our experimental finding that the continuous administration of rotigotine did not affect the sleep–wake cycle in either direction might appear unexpected. However, we believe that the absence of this effect is a genuine finding for the following reasons. Firstly, it would not appear to be due to the experimental methodology because the clear effects of nomifensine were obtained under the same experimental conditions, indicating that the test system was sensitive enough to detect potential effects of a drug on sleep architecture independent of its dopaminergic or noradrenergic activity. Furthermore, the results with nomifensine are in agreement with the findings of Lelkes et al. (1987) who described the arousal effects after repeated nomifensine administration in the rat. Secondly, the doses of rotigotine used would appear to be appropriate since clear CNS effects in the rat have been observed over the same dose range. For example, Bertaina-Anglade et al. (2006) describe an increase of locomotor activity at doses of 1 and 5 mg/kg using the same administration regimen. Similarly, Kehr et al., 2007 have described an increase in locomotor activity and a stable extracellular concentration of rotigotine in rat brain over 48 h after a single injection of a dose of 0.5 mg/kg of the slow release formulation as used here, suggesting that appropriate brain levels of rotigotine were achieved with the dosage regimen employed here, too. Although locomotor activity was not measured in the present test environment, the locomotor response to injections of the suspension have been shown to be highly reproducible under various experimental conditions (Scheller et al., 2005a). This suggests that the sleep–wake cycle in rats was not affected despite the animals being more active during periods of wakefulness. Thirdly, in the present study rotigotine was administered immediately before the dark phase of the light/dark cycle. The rationale for this was based on previous experiments suggesting that potential effects of dopaminergic compounds on sleep could be detected more readily during the dark phase than during the light phase (Lelkes et al., 1987, Olive et al., 1998). It is also known that brain melatonin concentrations are increased during the dark phase and are thought to antagonise dopaminergic systems (Sumaya et al., 2004; Zisapel 2001) which may explain the administration-time dependence of the effects on the sleep–wake cycle of dopaminergic compounds. However, no effects were observed with rotigotine in the present experiments, suggesting that the continuous administration of rotigotine does not interfere with endogenous rhythm-generating mechanisms despite stimulation of locomotor activity during the wake periods.

This result therefore suggests that the sleep–wake cycle remains generally unaffected by continuous dopamine receptor stimulation, whereas locomotor activity responds in a direct fashion to the presence of a dopaminergic agent. This is in line with the observation that the sustained administration of rotigotine does not result in a persistent increase in locomotor activity; instead, the enhancement of the locomotor activity of 6-hydroxydopamine lesioned rats is interrupted by periods of rest (Kehr et al., 2007). Thus, although arousal and stimulation of locomotor activity are both modulated by dopamine, they could be considered as two independent entities (Isaac and Berridge, 2003). This has already been demonstrated with the atypical stimulant modafinil which induces waking through dopaminergic mechanisms without increasing motor activity (Edgar and Seidel, 1997; Lin et al., 1992; Lin et al., 2000; Wisor and Eriksson, 2005). Furthermore, dopamine D_1 and D_2 receptor agonists administered i.c.v. have been shown to dose-dependently increase waking and suppress REM and slow wave sleep in the absence of locomotor activation (Isaac and Berridge, 2003). A similar shift in dose-dependence for the induction of arousal and hyperactivity has been described for amphetamine, i.e. low doses selectively increase waking without inducing motor hyperactivity (Berridge and Stalnaker, 2002).

Finally, it should be remembered that the present study was not designed to determine whether rotigotine can correct sleep disturbances linked to Parkinson's disease, nor to find a dose of rotigotine which affected the sleep–wake cycle. Instead, the study was designed to investigate whether a routinely used administration regimen of rotigotine which is known to have central effects in experimental models at clinically relevant doses, could affect the sleep–wake cycle. The results demonstrate that rotigotine, under these conditions of sustained administration, does not have any clear effects on the sleep–wake cycle in rats whereas its continuous administration in experimental models of Parkinson's disease using either the slow release formulation in rats (Scheller et al., 2005a) or an osmotic minipump in monkeys (Scheller et al., 2006a) not only improved the motor symptoms but also could prevent the generation of abnormal involuntary movements or dyskinesia under prolonged treatment (Scheller et al., 2005b). The plasma levels as obtained under those conditions were similar to those achieved clinically (Rose et al., 2007; Kehr et al., 2007).

The present study does not indicate to what extent the absence of effect on the sleep–wake cycle described here is specific to the receptor profile of rotigotine. Indeed, for a further understanding of the mechanisms involved in this respect, it will be interesting to compare the effects of continuous administration of rotigotine with other compounds that bind preferentially to dopamine D_3 receptors, such as PD 128907, on both the sleep–wake cycle and the locomotor activity in experimental models of Parkinson's disease.

In summary, the present results show that continuous dopaminergic stimulation with rotigotine at clinically relevant doses does not disturb the sleep–wake cycle in the rat and add evidence to previous experimental observations that this treatment regimen may have advantages over pulsatile treatments.

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